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Original Article

Serum activin-A as a prognostic biomarker for early and late mortality in critically ill patients with sepsis

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Abstract: Background: The primary objective of this present study was to investigate potential prognostic factors for early and late mortality in critically ill patients with sepsis. Methods: This single-center, prospective, non-interventional study was conducted in the ICUs of Taizhou People's Hospital. Consecutive adult patients suspiciously diagnosed with sepsis from June 2010 to June 2013 were prospectively enrolled in this study. The clinical data and laboratory tests among survivors and non-survivors at day 7 and day 28 were compared. Univariate and multiple logistic regression analyses were used for the analysis of independent prognostic factors for early and late ICU mortality. Results: Elevated activin-A level was significantly associated with lower survival rate both at day 7 and day 28 (P=0.002 and P<0.001 respectively) by Kaplan-Meier curves and log-rank test. The univariate and multivariate logistic regression analyses showed that activin-A expression at baseline was an independent prognostic factor for ICU mortality at day 7 (OR: 2.05, 95% CI: 1.22-3.32, P=0.009) and day 28 (OR: 2.68, 95% CI: 1.35-5.17, P=0.005) as well as the septic shock status. Conclusions: Our results revealed that serum activin-A concentration was a significant predicative biomarker for early and late mortality in critically ill patients with sepsis.

Keywords: Sepsis, activin-A, biomarker, mortality

Introduction

Various kinds of patients with life-threatening injuries were managed in intensive care units (ICUs) and high-technology medical equipment and multiple medications were needed for the evaluation and support for these patients. Sepsis has been considered as the major cause of morbidity or mortality in the hospitalized patients, especially in ICUs [1]. The mortality rate in patients with sepsis has decreased during the past decades, however, it still remains at a high stage in ICUs [2]. The investigation of valid prognostic biomarkers to support the outcomes predication has been ongoing for decades [3]. In hence, risk stratification biomarkers could be beneficial in the ICUs, including in the aspects of financial constraints, rational optimization of rather limited medical resources and the improvement of clinical decision-making [4]. In light of these findings, the evaluation and prognosis predication of sepsis plays a critical role in the clinical outcomes improvement. The Sequential Organ Failure Assessment (SOFA) score [5], the Acute Physiology and Chronic Health Evaluation (APACHE) II score [6] and the potential prognostic biomarkers [7, 8] including procalcitonin (PCT) and C-reactive protein (CRP) were widely reported to be closely associated with the severity of sepsis. Activin-A, a member of the transforming growth factor-β (TGF-β) superfamily, has been identified as a pleiotropic regulatory factor for cell development and function [9]. Serum activin-A concentration has been suggested as an indicator of disease severity by several animal and clinical studies [10, 11]. The primary objective of this present study was to investigate potential prognostic factors for early and late mortality in critically ill patients with sepsis.

Material and methods

Patients

This study protocol was approved by the Medical Institutional Ethics Committee of Jiangsu

province. This single-center, prospective, non-interventional study was conducted in the ICUs of Taizhou People's Hospital. Consecutive adult patients suspiciously diagnosed with sepsis from June 2010 to June 2013 were prospectively enrolled in this study. The diagnosis of systemic inflammatory response syndrome (SIRS), sepsis and septic shock was based on the criteria described by the 2001 American College of Chest Physicians/Society of Critical Care Medicine consensus [12]. Those patients with no ascertained clinical course, who comprised immunosuppression or missed data, were excluded from this study. Each patient included was required to offer the written informed consent for the blood sample obtainment.

Clinical data

The baseline demographic characteristics, primary diagnosis and the clinical scores of disease severity were collected and recorded on admission. The Simplified Acute Physiology Score (SAPS) II [13], SOFA score [5], Charlson comorbidity index [14] and APACHE II score [6] systems were calculated for the quantification of disease severity. The physiological variables including arterial oxygen tension/fractional inspired oxygen ratio (PaO_2/FiO_2), central venous oxygen saturation and lactic acid concentration were also collected on ICU admission. If an in vitro sensitivity pattern results suggested that the pathogenic microorganisms were sensitive to the administered antimicrobial drugs (at least one), then we considered the antibiotic treatment appropriate. In cases of culture-negative infection, treatment was considered appropriate if consistent with the local anti-infectious protocols.

Blood sampling

For all the enrolled patients, fasting blood was sampled within 24 h after ICU admission for baseline evaluation. The biochemical variables, such as PCT, CRP, lactate acid concentrations were all immediately conducted within 2 hours of blood collection at the laboratory in our hospital. The obtained samples in vacuum tubes containing EDTA were immediately centrifuged (3500 rpm, 10 mins) to separating the plasma and then stored at -80°C for further analysis.

Activin-A measurement by enzyme-linked immunosorbent assay (ELISA)

The quantification of serum activin-A concentration was conducted by using an ELISA kit (R&D Systems, USA). All the blood samples were detected in duplicate to ensure the intra-assay precision. The serum activin-A levels were measured by an investigator who was blinded to this study and patients' information according to the manufacturer's instructions.

Primary endpoint

Each patient was followed at least for 28 days in ICU or after discharge. In this present study, the mortality was evaluated at 7 days (D7) and at 28 days (D28) from ICU admission. D7 and D28 were used to define early and late mortality among the enrolled patients separately in this cohort.

Statistical analysis

GraphPad Prism 6.0 (GraphPad Inc., CA, USA) and SPSS 22.0 (SPSS, Inc., IA, USA) were used for data analysis in our study. Continuous data was presented as mean and standard deviation (SD) while categorical data as number (n) and percentage (%). Independent categorical data was analyzed by Chi-square test or Fisher exact test, whereas continuous variables between groups by Mann-Whitney U test or t test. Kaplan-Meier curves and log-rank test were used for the association between serum activin-A levels and the mortality. Univariate and multivariate logistic regression analyses were used for early and late mortality evaluation. All statistical tests were bilateral probability and $P<0.05$ was considered significant.

Results

Patient cohort

312 eligible patients in ICU were prospectively enrolled in this study protocol during June 2010 and June 2013. 25 of them were excluded for various reasons (8 discharged from ICU within the first 48 h, 7 missed clinical data, 7 refused to cooperate, 3 were with laboratory technical issues) and 287 were ultimately included into the final analysis with available blood samples. The clinical characteristics and serum biomarkers were described in **Table 1**.

Table 1. Baseline characteristics, clinical scoring and biomarkers of critical ill patients with sepsis

Variables	Day 7		Day 28	
	Survivors (n=216)	Non-survivors (n=71)	Survivors (n=179)	Non-survivors (n=108)
Age	56.3 ± 15.7	62.4 ± 16.2[b]	56.1 ± 12.9	60.6 ± 17.1[a]
Gender (%)				
Male	118	39	89	68
Female	98	32	90	40
Presence of sepsis (%)				
Community-acquired	141 (65.3)	43 (60.6)	114 (63.7)	70 (64.8)
Hospital-acquired	75 (34.7)	28 (39.4)	65 (36.3)	38 (35.2)
Site of infection (%)				
Respiratory	103 (47.7)	34 (47.9)	89 (49.7)	48 (44.4)
Abdominal	45 (20.8)	17 (23.9)	41 (22.9)	21 (19.4)
others	68 (31.5)	20 (28.2)	49 (27.4)	39 (36.2)
Clinical scoring				
APACHE II score	19.7 ± 4.6	24.3 ± 5.1[b]	19.5 ± 5.3	23.1 ± 4.1[b]
SAPS II score	52.9 ± 15.3	78.3 ± 20.1[b]	51.8 ± 13.7	71.4 ± 16.4[b]
SOFA score	9.3 ± 4.1	12.1 ± 4.6[b]	9.1 ± 3.9	11.5 ± 5.0[b]
Charlson comorbidity index score	2.8 ± 0.7	3.0 ± 0.8[a]	2.9 ± 1.1	2.8 ± 1.3
Organ support therapy (%)				
Respiratory	154 (71.3)	65 (91.5)[b]	121 (67.6)	98 (90.7)[b]
Renal	43 (19.9)	40 (56.3)[b]	24 (13.4)	59 (54.6)[b]
Haemodynamic	128 (59.3)	60 (84.5)[b]	123 (68.7)	65 (60.2)
Septic shock (%)	97 (44.9)	43 (60.6)[a]	73 (40.8)	67 (62.0)[b]
Central venous oxygen saturation (%)	66.1 ± 9.8	65.7 ± 11.3	66.2 ± 12.1	65.7 ± 14.0
PaO2/FiO2 ratio	254.7 ± 187.3	240.6 ± 165.2	251.9 ± 201.4	250.1 ± 190.4
Serum biomarkers on ICU admission				
CRP (mg/dL)	33.4 ± 22.5	55.7 ± 43.1[b]	28.6 ± 21.6	56.0 ± 39.8[b]
Lactic acid (mmol/L)	2.7 ± 1.9	4.5 ± 3.4[b]	2.3 ± 1.6	4.5 ± 3.7[b]
IL-6 (pg/mL)	89.3 ± 35.5	111.5 ± 44.7[b]	95.4 ± 41.5	93.8 ± 51.4
PCT (μg/L)	1.2 ± 0.9	2.3 ± 2.0[b]	1.4 ± 1.0	1.6 ± 1.2
Activin-A (pg/mL)	387.5 ± 226.7	613.5 ± 412.6[b]	406.4 ± 264.5	504.7 ± 253.1[b]
Germ categories (%)				
Gram-negative	129 (59.7)	39 (54.9)	110 (61.5)	58 (53.7)
Gram-positive	85 (39.4)	31 (43.7)	66 (36.9)	48 (44.4)
Fungi	2 (0.9)	1 (1.4)	3 (1.7)	2 (1.9)
Plurimicrobial	60 (27.8)	23 (32.4)	53 (29.6)	30 (27.8)
Length of stay in ICU (d)	11.9 ± 5.7	12.4 ± 7.9	11.8 ± 6.3	12.2 ± 5.8

ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; CRP, C-reactive protein; IL-6, interleukin-6; PCT, procalcitonin; PaO2/FiO2, arterial oxygen tension /fractional inspired oxygen ratio. *P*-values were calculated by Chi-square test, Fisher exact test, Mann-Whitney U test or t test. [a]P<0.05; [b]P<0.01.

Clinical outcomes at day 7

At day 7, 216 of all the 278 patients were still alive and characteristics among survivors and non-survivors were compared for the evaluation of risk factors for ICU mortality. The non-survivors within 7 days from ICU admission were presented with significantly older age (P<0.01), higher APACHE II (P<0.01), SAPS II (P<0.01), SOFA (P<0.01) and Charlson comorbidity index scores (P<0.05). The incidence of septic shock (P<0.05) and rate of organ sup-

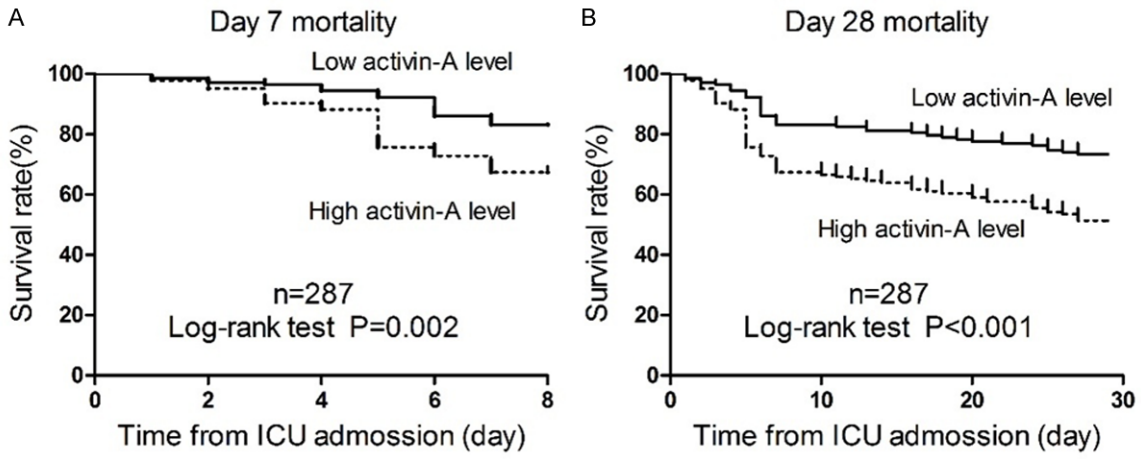

Figure 1. Kaplan-Meier curves of 7-day (A) and 28-day (B) mortality in critical ill patients with sepsis stratified by median baseline serum activin-A level. High serum activin-A level was significantly associated with higher 7-day and 28-day mortality by log-rank test (P<0.01).

port therapy (respiratory, renal and hemodynamic) (P<0.01) in non-survivors were more frequently in comparison with those survivors. Elevated baseline serum expressions of CRP (P<0.01), IL-6 (P<0.01), lactic acid (P<0.01), PCT (P<0.01) and activin-A (P<0.01) were also closely associated with higher 7-day mortality in sepsis patients.

Clinical outcomes at day 28

In the total cohort, 108 enrolled patients died within 28 days from ICU admission with a 28-day mortality of 38.8%. The comparison between survivors and non-survivors at day 28 showed significant differences in age, APACHE II, SAPS II, SOFA scores, respiratory support, renal support rate and septic shock incidence (P<0.05). The serum concentrations of CRP, lactic acid and activin-A at baseline also differed significantly between these two subgroups (P<0.01).

Activin-A levels and ICU mortality

To evaluate the possible association between activin-A and ICU mortality at day 7 and 28, Kaplan-Meier survival curves were generated with the median value of activin-A as the threshold. Log-rank test analysis suggested that the survival rate was significantly higher in the patients with high activin-A levels (≥median value) than those with low activin-A levels (<median value) both at day 7 and 28 (see **Figure 1A** and **1B**, P=0.002 and P<0.001 respectively).

Predicator for ICU mortality by univariate and multivariate analyses

Finally, in univariate and multivariate analysis as shown in **Table 2**, activin-A expression at baseline was independently associated with increased risk of mortality at day 7 (OR: 2.05, 95% CI: 1.22-3.32, P=0.009) as well as the septic shock status (OR: 2.39, 95% CI: 1.43-4.24, P<0.001) and SAPS II score (OR: 2.63, 95% CI: 1.64-4.33, P<0.001). The multivariate logistic regression analyses also revealed that serum activin-A expression (OR: 2.68, 95% CI: 1.35-5.17, P=0.005), SOFA score (OR: 5.45, 95% CI: 2.18-8.06, P=0.001) and septic shock status (OR: 0.38, 95% CI: 0.20-0.72, P=0.003) were independently associated with ICU mortality at day 28 (see **Table 3**).

Discussion

In this context, the evaluation of serum biomarkers might present the advantage of very low pre-analytical constraints and facilitate their application for prognosis predication on a routine basis. CRP, IL-6 and PCT, the common biomarkers for inflammation or infection, have been involved in the pathophysiology of sepsis and routinely utilized in the diagnosis, prognosis predication or therapeutic efficacy monitoring [15]. However, they were known to be far from perfect biomarkers and whether they could actually act as prognostic factors still remained conflicting [16, 17]. Our final results by multivariate analyses revealed that serum CRP, PCT and IL-6 concentrations were not

Table 2. Univariate and multivariate analyses of day 7 mortality in critically ill patients with sepsis

	Univariate		Multivariate	
Variables	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	0.99 (0.97-1.01)	0.076		
APACHE II score	1.51 (0.82-1.83)	0.187		
SAPS II score	6.32 (4.22-9.78)	<0.001	2.63 (1.64-4.33)	<0.001
SOFA score	0.78 (0.46-1.29)	0.328		
Charlson comorbidity index	2.52 (1.71-3.76)	0.002	1.43 (0.90-2.24)	0.127
Respiratory support	0.88 (0.54-1.43)	0.401		
Renal support	1.08 (0.63-1.88)	0.817		
Haemodynamic support	0.73 (0.43-1.31)	0.221		
Septic shock	5.54 (3.53-8.86)	<0.001	2.39 (1.43-4.24)	<0.001
CRP (baseline)	1.62 (0.83-2.99)	0.143		
IL-6 (baseline)	1.53 (0.93-2.55)	0.112		
Lactic acid (baseline)	4.81 (3.02-7.57)	<0.001	1.04 (0.62-1.93)	0.772
PCT (baseline)	3.83 (2.51-6.04)	<0.001	1.42 (0.77-2.83)	0.158
Activin-A (baseline)	4.63 (3.15-6.77)	<0.001	2.05 (1.22-3.32)	0.009

APACHE, Acute Physiology and Chronic Health Evaluation; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; PCT, procalcitonin; CRP, C-reactive protein; OR, Odds ratio; CI, Confidence interval.

Table 3. Univariate and multivariate analyses of day 28 mortality in critically ill patients with sepsis

	Univariate		Multivariate	
Variables	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	0.87 (0.53-1.42)	0.564		
APACHE II score	3.11 (1.41-7.23)	0.007	2.41 (0.93-6.51)	0.078
SAPS II score	4.35 (2.13-8.63)	<0.001	3.51 (0.97-6.53)	0.097
SOFA score	6.07 (3.08-9.21)	<0.001	5.45 (2.18-8.06)	0.001
Respiratory support	1.32 (0.38-5.77)	0.598		
Renal support	1.24 (0.46-3.66)	0.514		
Septic shock	0.46 (0.25-0.77)	0.004	0.38 (0.20-0.72)	0.003
CRP (baseline)	1.21 (1.07-1.33)	0.008	2.31 (0.72-4.21)	0.112
Lactic acid (baseline)	1.64 (0.56-4.18)	0.289		
Activin-A (baseline)	3.18 (1.81-5.45)	<0.001	2.68 (1.35-5.17)	0.005

APACHE, Acute Physiology and Chronic Health Evaluation; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; CRP, C-reactive protein; OR, Odds ratio; CI, Confidence interval.

independent predicators for day-7 mortality in critically ill patients with sepsis, which was quite in accordance with other data [18]. To our knowledge, our study firstly demonstrated that activin-A expression at baseline was significantly associated with early (day 7) and late (day 28) mortality in critically ill patients with sepsis. The results from this cohort of patients showed that increased activin-A level was an independent predicator for sepsis mortality. We suggested that the monitoring of serum activin-A level can be used for risk stratification in ICU patients with sepsis.

Previous animal model studies have indicated that activin-A releasing can be investigated within 40min after lipopolysaccharide injection followed by the IL-6 release and before tumor necrosis factor-α (TNF-α) [19, 20]. It suggested that the release of activin-A acted as an important component of the innate immune system in response to acute inflammation. Serum activin-A was also involved in proinflammatory functions by provoking other inflammatory mediators releasing including IL-6, IL-1β, TNF-α [21]. Furthermore, activin-A could also performed an immunoregulatory function by inhibiting IL-6 release, caspase-1 and the caspase-1-induced inflammatory cascade [22, 23]. In general, activin-A played a critical role in inflammatory actions and immunity system by proinflammatory and immunoregulatory activities, which was quite similar with the mechanisms of immunological response in sepsis [24]. On the basis of these findings, some researchers have suggested serum activin-A as a potential effective biomarker for sepsis conditions instead of other inflammatory biomark-

ers that only reflect the inflammatory status [24]. This is consistent with our results that serum activin-A concentration was an independent risk factor for early and late ICU mortality in patients with sepsis instead of CRP, IL-6 and PCT. The occurrence of septic shock was a significant prognostic factor for both early and late ICU mortality, which was in accordance with other previous studies [25]. Previous data from animal or small clinical studies concerning whether activin-A was closely correlated with the clinical outcomes of patients with sepsis still remains controversial [26, 27]. Based on this single center, observational population study, we found that elevated serum activin-A concentration was a significant risk factor for high day-7 and day-28 mortality in ICU by univariate and multivariate analysis.

In conclusion, our results revealed that serum activin-A concentration was a significant predicative biomarker for early and late mortality in critically ill patients with sepsis.

Disclosure of conflict of interest

None.

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